BRINGING 'BLUE SKY BIOLOGY' DOWN TO EARTH: LINKING NATURAL PRODUCTS RESEARCH WITH COMMERCIALIZATION.

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ABSTRACT

There are thousands of bioactive phytochemicals with potential or established nutraceutical, medicinal or pharmaceutical applications. The challenges in developing crops for commercial extraction of bioactive compounds are twofold: 1) which plants are realistic candidates for research directed at commercialization, and 2) for a selected phytochemical or species, what additional market-related factors must be considered in developing a new crop? Using both existing medicinal crops and the CFS experience with *Taxus canadensis* to provide examples, some market factors, which must be considered prior to commercialization, are discussed.

General bioproduct factors include: availability of a cheaper product elsewhere from the same species; existence of another species with a higher bioactive compound concentration; existence of a synthetic alternative to the naturally-sourced phytochemical market; and existence of patents covering bioproduct extraction and use.

A second group of market factors are specific to the role and suitability of an industrial collaborator proposing to fund R&D activities. Analogous to an industrial partner's due diligence of an R&D proposal, the R&D partner must likewise gauge the potential commercial partner's fitness. Assessments are needed on factors like: the company's knowledge of the marketplace; their capacity to sustain the proposed R&D funding; whether their intent is to market raw biomass or a value-added product; the impact of their exploitation on sustainability of the resource; and how they propose to handle exclusivity and proprietary information.

Finally, an economic case has to be made for cultivation as a profitable alternative to wildcraft harvesting. Cropping must be shown to be economically viable by addressing two issues: the capacity of the woodland resource to meet the demand, and the price of cultivated biomass. Some of the advantages and economics of *T. canadensis* nursery cropping versus woodland harvesting are presented.

Introduction

One estimate of medicinal plant use suggests that over 35,000 species are used worldwide (5). Convention-al Western medicine relies heavily on phytomedicines: 50-60% of pharmaceutical commodities contain natural products or are synthesized from them, and 10–25% of prescription drugs contain one or more natural bioactive compounds (16). The wide spectrum of choices for development of new crops for the pharmaceutical/medicinal industry leads immediately to two questions: (1) which plants and compounds from among the large number of potentially valuable bioactive compounds are realistic candidates for research directed at commercialization, and (2) having selected a phytochemical or species, what additional market-related factors must be considered? This presentation focuses on some of the aspects surrounding the second question using examples of commercially produced bioactive crops and our experience at the Canadian Forest Service–Atlantic Forestry Centre (CFS–AFC) with *Taxus canadensis*, commonly known as ground hemlock or eastern yew.

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The Case for a Commercial *Taxus* Crop

A cursory analysis of the commercial potential of yew, and particularly *T. canadensis*, suggests that entry into the pharmaceutical marketplace should be straightforward. Paclitaxel, also called Taxol®, is a well-established cancer drug that has been sold by Bristol Meyers Squibb (BMS) for clinical use since 1992, and has been called the largest selling anti-cancer drug in the world (6). Taxol® and the closely related taxane Taxotere® (docetaxel, produced by Aventis) had sales in 2001 of $2.3 billion USD (2). Recently, BMS's exclusivity has ended, resulting in generic paclitaxel available for sale by other large pharmaceutical companies like Ivax, Abbott, and Mylan. Market demand is expected to grow by 10% each year for at least the next decade and new, second-generation paclitaxel formulations and analogs may serve to lengthen the compound's lifespan (2).

Although the paclitaxel molecule has been synthesized, it is an expensive process. Fermentation and cell culture methods are still under development. Plant biomass continues to be the most economical source of the drug (2), but woodland sources are increasingly in short supply globally (13). Commercial nurseries in the United States produce millions of plants for sale in the horticultural market, but our discussions with industrial sources indicate that the amount of nursery biomass remaining for sale to the taxane industry is inadequate to meet the demand.

The *Taxus* "domestication" project was initiated in 1997 with the goal of rearing *T. canadensis* as a hedged or row crop for paclitaxel production. The term "domestication" in the current context may be defined as the inter-related phases in the process whereby a wild species is genetically selected to produce elite cultivars, propagated, then reared as an industrial crop. Details of the methods being used are summarized in an accompanying PGRSA presentation (see Smith and Cameron, this proceedings). The project was initiated in response to the interest of an industrial client who was ultimately unable to find a successful path to commercialization and thereby raise the funds necessary to provide adequate support for the project. During the years following those first discussions, a number of other prospective collaborators — companies both large and small — followed the same pattern, initially enthusiastic about commercialization, only to be subsequently frustrated in their attempts to craft a successful strategy that would permit product sales. The search to find support for the *Taxus* domestication project, now funded, has been the source of valuable experience on the R&D/phytopharmaceutical industry interface, and other important factors to consider prior to collaboration.

Important Bioproduct Market Factors

To find a suitable client (or decide whether it is feasible to seek one out), the R&D partner must acquire some elementary knowledge about the commercial aspects of the niche into which the candidate bioproduct must fit, preferably even before approaching potential collaborators. As a starting point, an estimate of the longevity of the bioactive compound as a saleable marketplace commodity is important. If product sales are likely to continue for an indefinite period, as may be the case with many of the well-known nutraceuticals, such as glucosamine or echinacea, then long-term consumer demand may be assumed. In contrast, the lifespan of compounds such as paclitaxel may be shorter, as new, more effective drugs and therapies emerge to replace them. The significance of a bioactive compound's product life is that timing is an important component in planning realistic research objectives. Several additional basic questions about the economic consequences of the biology also need to be asked.

a) Can the same species be harvested and the crude product extracted more cheaply elsewhere in the world? Many species have a wide distribution, some worldwide, and biomass containing the same bioactive compounds may be collected in different regions. Alternatively, and particularly if wild-harvested biomass is in short supply and/or prices are sufficiently high, it may be possible to cultivate from seed as agricultural or agro-forestry crops, plants that are suited to one or more local environments, thereby making cropped biomass widely available. An added advantage is that cultivated plants can be fertilized, tended, selected and bred to produce uniform crops of elite cultivars with a higher bioactive content. Species such as American ginseng (*Panax quin-quefolius*), evening primrose (*Oenothera biennis*), and cranberry (*Vaccinium macrocarpon*) are only three of numerous examples where cultivation has replaced wildcrafting.

The production of paclitaxel presents an interesting hybrid of commercial and biological constraints. Because the North American pharmaceutical industry is the main market for paclitaxel sales, US Food and Drug Agency (FDA) regulations apply. Introducing natural products into the US pharmacopoeia is a highly regulated and complex process (9). High standards of manufacturing (cGMP) are required and a company's complete manufacturing process must be documented in a drug manufacturing file (DMF II), specifying the species and plant part, geographical location and processing of the raw material (15). The consequence is that, even though paclitaxel can be extracted from more than one *Taxus* species, once a particular species has been specified, it is not a trivial matter to amend the DMF II to change the source material. Wildcrafted material is also subject to an FDA sustainability requirement through the US Code of Federal Regulations (21 CFR, part 25 'Environ-mental Impact Considerations'). Biomass collection must be demonstrated to be sustainable and thereby subject to "categorical exclusion" from an EI assessment (i.e., wild harvesting must be shown to have no effect on abundance or biodiversity) which complicates the addition or substitution of a species.

b) Does another plant species (or genus) differing from the locally available species, but with the same suite of phytochemicals perhaps in higher abundance, exist elsewhere? Many phytochemicals occur widely in different plant families, with the commercial outcome that wildcraft harvesting or cultivation in a competitive market may be more economically feasible elsewhere with a species other than the one available locally. Mayapple (Podophyllum peltatum), although distributed widely in North America, is not the main source of podophyllotoxin, which is found in greater quantity in the Himalayan species Podophyllum hexandrum (11), now placed on the Convention on International Trade in Endangered Species (CITES) list due to over-harvesting (13). A number of other species are reported to contain minor amounts as well (14). Similarly, camptothecin, an anti-cancer alkaloid, is found in different trees from China (Camptotheca acuminata) and India (Mappia foetida or Nothapodytes foetida) (7). Diverse plant distribution potentially can also be of positive benefit, permitting a greater latitude in the choice of which plants to cultivate, as is the case, for instance, in the production of the nutraceutical antioxidant ellagic acid, which occurs in commercial strawberry, raspberry, and blackberry cultivars (1).

Paclitaxel occurs in varying amounts in all *Taxus* species (4), as well as some endophytic fungi (17). The taxanes are a family of well over 350 diterpenoid compounds (3), many of which are unique to a single species. Like many other phytomedicinal species, the *Taxus* species in several of the major wildcraft harvesting regions (India, Nepal, China) have already been placed on the CITES list of at-risk or endangered species (13).

The potential of *T. canadensis* to substitute for other *Taxus* species is considerable. First, the commercially available horticultural *Taxus* varieties are derived from plant breeding crosses chosen for their form, color, etc. and not taxane content and, therefore, have only a limited potential for

improved yields through genetic selection. *T. canadensis* has an extensive natural range and, therefore, a wide genetic base from which individuals with exceptional growth and taxane levels may be selected. Second, one taxane found uniquely in ground hemlock, 13-acetyl-9-dihydrobaccatin III (9-DHB), is present in high abundance and can be used for semi-synthesis (12). Despite these advantages, a major unknown in the commercialization of *T. canadensis* is the lack of knowledge about the locations and volumes of alternative sources of cultivated biomass from either ornamental or woodland stock plants.

c) Is there an identical, easily synthesized compound that can be commercially produced more economically than the naturally sourced phytochemical? As noted in the Introduction, since over half of all medicines come from natural sources (or have in the past), it is reasonable to expect the substitution of cheaply synthesized chemically identical compounds, or even analogs of the natural material modified to improve their medicinal properties. One of the best examples of commercial chemical evolution is aspirin, or acetyl-salicylic acid which is the modern substitute for the salicylates traditionally used for pain relief and found in various members of the willow family (8).

Implicit to the notion of an easily synthesized alternative is that the bioactivity derives from a single compound. Often synergistic effects are found to occur when phytomedicinal extracts are used. The therapeutic effect(s) in medicinal products such as echinacea (*Echinacea pallida*) is caused by a combination of different compounds in the plant. It is unlikely that synthetic alternatives are to be easily found for such species, which makes a stronger case for their continued commercial wildcrafting and/or cultivation.

Although it is possible to produce taxanes, both through direct synthetic chemical methods and bio-reactor culture (17), neither route appears to be used extensively at present (2). Biomass remains the predominant resource for taxane supplies. As noted previously, the two advantages of genetic diversity and the presence of a unique taxane potentially give *T. canadensis* a competitive advantage as an intensively cultivated Canadian crop over other species in regions where labor costs are low and/or biomass is in short supply. Several industrial sources have indicated to CFS–AFC that the comparatively high cost of woodland harvested ground hemlock biomass is the chief disadvantage of sourcing Canadian purchases. Even though biomass is allegedly scarce elsewhere, *T. canadensis* must be competitively priced.

d) Will commercialization of the compound(s) or bioactive derivatives be limited significantly by existing patents and/or their licensing costs? A search of the existing patent literature should be regarded as a mandatory part of any new commercially oriented R&D project. Small searches may be performed without charge on both the US and Canadian internet patent sites, and patent information is useful in identifying the names of companies in the marketplace, the segment of the market they serve, and which ones might be interested commercial exploitation of a particular bioproduct. The internet also can quickly provide a snapshot of financial and technical information on specific companies.

A search performed at CFS–AFC in the spring of 2001 on the terms "Taxol", "paclitaxel" "taxane" and "Taxus" produced a list of over 1800 US and Canadian patents on items ranging from biomass drying ovens, through extraction, semisynthesis, and purification methods to pharmaceutical formulations and new taxane analogs. Because *T. canadensis* biomass contains both paclitaxel and 9-DHB, the patent literature was of particular interest to us.

The practical significance of an awareness of the patents held by a particular pharmaceutical company is that the information helps to determine which taxanes they are likely to find of interest. A company owning only the patents for efficient paclitaxel extraction is less likely to be interested in 9-DHB and therefore may not regard *T. canadensis* foliage as particularly valuable in comparison with

other *Taxus* species. A second company whose patents would allow efficient paclitaxel semi-synthesis from 9-DHB may value ground hemlock highly as they may need to purchase only half or less the amount of foliage or crude extract to meet their paclitaxel production target.

The industrial collaborator's suitability

It is helpful to focus on the concept that "the customer is always right". An R&D partner and the industrial collaborator are, in a very real sense, each other's customer. Getting the right fit to the market and to each other maximizes the chances for both successful R&D and subsequent commercialization, which are the goals for both partners. This means that the R&D partner should ask some basic questions about the qualifications of a prospective business partner in the same way that the potential collaborator appraises the proposed research.

a) Does the company that intends to finance the research and development work have adequate knowledge of the market in which they intend to sell the end product? In discussions at CFS–AFC with a number of potential partners, we found that their level of market knowledge varied widely, from the extremes of having heard or read positive (and sometimes unrealistic) information through the public media to a detailed and proprietary appreciation of the paclitaxel market. The reasons for their interest were just as diverse, ranging from businesses with a general desire to expand into new product lines to those already in the taxane industry with very specific requirements.

To submit a realistic business plan to a board of directors and/or an external funding agency which is likely to include funding for the R&D project, the industrial collaborator must be able to show profitability within a reasonable period, or some measure of a competitive edge that makes the investment in research worthwhile in comparison to other alternatives. The better their acquaintance with the market is, the sooner and more likely it is that a collaborative agreement can be successfully completed.

b) Does the industrial collaborator have the size and infrastructure to sustain the proposed R&D funding?

A collaborator does not have to be a large corporation. However, if the company is small and new, their cash flow may be limited. Typically, they may be attempting to put together a combination of loans, grants, and sales agreements with other industrial partners. It is advantageous for the R&D partner to see (and understand) their business plan before signing a collaborative agreement. Doing so can help highlight potential problems, such as the undue dependence of cash flow on, for instance, yet-unsigned contracts for processing biomass or a need for government assistance not yet granted. The capacity of a small company to immediately start operation and generate profit is important. Their infrastructure, or lack of it (for example, proposed cropland acquisition or purchase of specialized processing equipment as part of the business plan) can delay them getting started.

The potential concerns are different in a collaboration with a large company (for instance, a corporation supplying pharmaceutical-grade paclitaxel to a major drug company). Such a company, having already invested in the taxane market at another location, may wish to cultivate or do processing elsewhere. Particularly in dealing with a company already in the taxane marketplace, signing a non-disclosure agreement can be a valuable asset. It allows the R&D partner access to market information not available in the public domain.

c) Does the industrial collaborator intend to market the raw biomass or process it into a value-added product? Generating high-quality employment in eastern Canada is of great interest to both the regional and federal governments. Biomass harvesting is a valuable source of income for rural, seasonally employed people. High-end employment (chemists, process engineers) accrues at the

value-added post-harvest stage of *Taxus* biomass drying and processing. The infrastructure exists in eastern Canada to completely process, semi-synthesize, and purify paclitaxel to pharmaceutical grade, reportedly at competitive prices. Nonetheless, the express-ed intention of one potential industrial collaborator was to send all biomass overseas for all further processing. While it may make business sense to process offshore, it becomes more difficult to find a good fit with such a company. They also risk complicating their biomass supply strategy, as several provincial governments are in the midst of legislating restrictions on transporting unprocessed biomass harvested on Crown land outside the province where it was harvested.

d) What impact will the industrial collaborator's entry into the marketplace have on the resource? Part of the CFS mandate is to promote sustainable use of forest resources. An important part of the *Taxus canadensis* project has been the development of sustainable harvest guidelines. These guidelines are discussed elsewhere (Smith and Cameron, in this proceedings). Their intent is to prevent over-harvesting of existing woodland *Taxus* biomass, especially during the crop development R&D period prior to harvesting significant amounts of elite nursery biomass. It would be in direct conflict of CFS policy to partner with any industrial collaborator unwilling to adhere to sustainable harvest practices.

e) How does the industrial collaborator propose handling exclusivity and proprietary information? In return for supplying research funds, it is reasonable for the collaborator to expect some degree of exclusive access to the findings that result from the work. The potential conflict(s) between commercialization and the public good presents an interesting situation. The process of reconciling commercial goals with government R&D policy is an issue too large to discuss here. However, one of the reasons for our initial choice from among several prospective industrial partners, and the practical accommodations subsequently negotiated with our industrial collaborator are worth noting.

Concerning exclusivity, project funding was offered by different private companies on several occasions before an agreement was finally signed. The alternatives were: (1) to sign on with a single pharmaceutical supplier to give them exclusive rights to the domestication technology, or (2) to link with a local entrepreneur who could, in turn, market taxanes to those suppliers based on several biomass and (or) processing contracts. We chose the second alternative on the basis of the government perspective that choosing a company supplying more than one customer would be more beneficial overall to the taxane industry in eastern Canada.

With regard to intellectual property (IP), under the collaborative agreement contract between Natural Resources Canada and the industrial collaborator, all IP at CFS obtained before the agreement was signed remains CFS property. IP developed during the funding period is to be held jointly, which is appropriate since the CFS in-kind contribution equals the contract funds. For the *Taxus* domestication project, this means that the 1300 individual cultivars or plants continue to belong to the government. The industrial collaborator has the exclusive right to commercialize the elite cultivars, plus all propagation and growing techniques that are developed during the life of the agreement in whatever way they deem to be appropriate. There are, however, a few limitations. One of the main ones is that neither the plant material nor technology may be taken out of Canada without prior permission of the CFS since the Canadian taxpayer is a co-owner. The intent is to prevent export to other countries where, for example, the cost of land or labor may be cheaper, with the concomitant loss of jobs in Atlantic Canada. This fulfills the mandate of the CFS to promote development of the local economy.

Conclusion: the Economics of *Taxus canadensis* Domestication and Cultivation

To make an economic case for *T. canadensis* cultivation, two issues need to be addressed: the capacity of the woodland resource to meet the demand, and the price of cultivated biomass.

First, concerning demand, commercial harvester estimates suggest that the annual limit for sustainable harvest of biomass in eastern Canada is approximately 5–6 million kg fresh wt per year. Drying and processing that amount of green biomass would yield 1.5–1.7 million kg dry wt per year, sufficient to produce 150–170 kg paclitaxel annually. The world market demand is currently about 300 kg per year, with, as previously noted, a predicted rise over the next decade to perhaps 1000 kg per year (10% increase per annum). Discussions with pharmaceutical supply companies indicate that several large suppliers are each interested in acquiring *T. canadensis* biomass or crude extract equivalent to over 100 kg of paclitaxel. If more than one pharmaceutical client were to enter the eastern Canadian market, the woodland resource could not meet the demand.

Second, with regard to price, the current cost of woodland-collected *T. canadensis* biomass is approximately $11.00 CAD/kg dry wt. According to industrial buyers, similar quality biomass is reportedly available from Asia for approximately $7.00–8.00 CAD/kg dry wt. A kilogram of paclitaxel, though selling at perhaps $200,000 CAD or more at 99% purity, is only worth $32,000 CAD calculated based on the paclitaxel content of dried, unextracted biomass. The equivalent overseas price is about $22,000 CAD/kg dry wt.

The price also depends on improved biomass quality and/or nursery growth rate which, in turn, requires demonstration of genetic diversity in wild *T. canadensis*. As Table 1 indicates, even in a small sample (48 plants), taxane content varies almost twofold above and below the mean. Similarly, in Figure 1, which shows a small number of different clones (35 clones) grown in a common greenhouse environment, there was a fivefold difference in biomass accumulation after four years growth.

Taxane	% of dwt		
	Mean	Min.	Max.
PAC	0.040	0.018	0.076
9-DHB III	0.119	0.023	0.251
10-DAB III	0.024	0.000	0.056
All Three	0.184	0.059	0.375

Table 1. Variation in taxane concentrations in 48 4-year-old plants sampled from five sites in Quebec environment (source: Bioxel Pharma data)

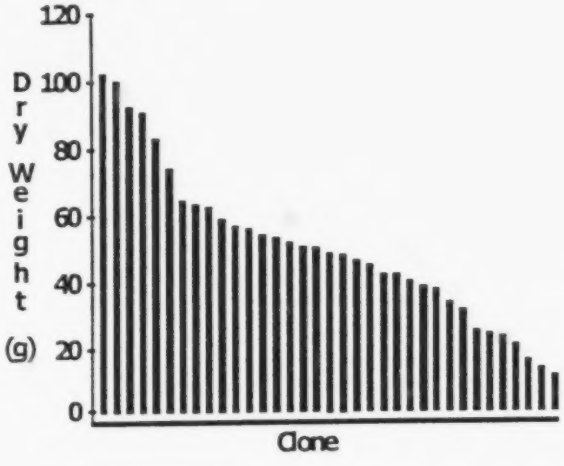

Figure 1. Total plant biomass for 35 clones of plants grown in a common nursery (source: unpublished CFS data)

Table 2 shows estimated biomass volumes and prices based on a comparative analysis done at CFS. Neither wildcrafted biomass nor a nursery crop produced from cuttings taken from wild stock plants would be competitive with the price overseas biomass (provided it is available and not in short supply). However, cultivated crops using cultivars selected for elevated taxane levels are price competitive, even if only very modest assumptions are made about the magnitude of crop improvement are made. Using a conservative assumption of only a doubled taxane content, an analysis is given in Table 2.

	TARGET: 100 kg. of paclitaxel per year from:		
	Woodland harvested biomass	Non-elite cultivated crop	Elite cultivar crop: 2x paclitaxel content
Biomass needed (kg dry wt)	1.0 million	1.0 million	0.5 million
Harvest or cultivation and drying costs	$8.8 million	$19.9 million	$5.7 million
Cost per kg of biomass	$8.80	$19.90	$11.30
Cost per kg paclitaxel	$25,100	$56,800	$16,300

Table 2. Price and volume estimates for *Taxus canadensis* biomass produced by various means. (Cameron, Smith and Smith (2001), unpublished)

Therefore, even assuming future scarcity does not limit biomass purchase from overseas sources, a strong case can be made for commercialization, provided using a cultivated product with equal or better quality sold for the same or less cost. Our analysis of biomass costs from the three sources suggests that the biomass component of paclitaxel costs can be decreased by almost 50%. Since biomass accounts for 30–50% of total production costs, the savings are potentially significant.

The *Taxus* domestication project has demonstrated for us that an R&D partner needs to be aware of market realities in order to focus research objectives, make pragmatic decisions to eliminate non-essential though interesting parts of a study, and choose among alternative routes to meet commercial objectives with realistic timelines. Equally important is a critical examination of the market opportunity and competition, and the strengths and weaknesses of prospective industrial collaborators. Finally, a good economic case for domestication is required. This presentation has focused on the phytopharmaceutical market. However, the barriers to successful collaboration and the commercial or market intelligence needed to address them should generally apply to the entry of any other plant bioactive product into the industrial marketplace.

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